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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,254	08/14/2008	Doug Bettenhausen	119557-00402	6435

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EXAMINER	
DRAPER, LESLIE ALEXANDRA R	
ART UNIT	PAPER NUMBER
1629	
MAIL DATE	DELIVERY MODE
08/15/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/588,254	BETTENHAUSEN ET AL.
	Examiner	Art Unit
	Leslie A. Royds Draper	1629

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☒ Claim(s) *1 and 24-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02Nov06; 08Jan08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26 are presented for examination.

Acknowledgement is made of the present application as a National Stage (371) entry of PCT Application No. PCT/US2005/018757, filed May 27, 2005, which claims benefit under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/608,951, filed May 28, 2004.

Applicant's Information Disclosure Statements (IDS) filed November 2, 2006 (one page) and January 8, 2008 (one page) have each been received and entered into the present application. As reflected by the attached, completed copies of form PTO/SB/08A (two pages total), the Examiner has considered the cited references, except for the references designated "CA" and "CB" on the Information Disclosure Statement filed November 2, 2006. The information disclosure statement filed November 2, 2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because Applicant has failed to provide the relevant publication information for the references designated "CA" and "CB". It has been placed in the application file, but the information referred to therein as references "CA" and "CB" has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Requirement for Restriction/Election

Applicant's election **without traverse** of the species of (1) gastrointestinal malignancies as the single disclosed species of disease for which the subject is receiving radiotherapy and (2) colorectal cancer as the single disclosed species of gastrointestinal malignancy for which the subject is receiving

radiotherapy, for examination on the merits, in the reply filed May 23, 2011, is acknowledged by the Examiner.

Therefore, for the reasons *supra* and those made of record at p.2-5 of the previous Office Action dated April 21, 2011, the requirement remains proper and is hereby made **FINAL**.

The claims corresponding to the elected subject matter are claims 1-26 and such claims are herein acted on the merits.

Objection to the Claims

Claims 1, 24, 25 and 26 are each objected to for reciting a comma between the word "comprising" and the word "administering", which is grammatically awkward. Correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The phrase "in need thereof" as used to describe the patient subject to the instantly claimed method renders the claims indefinite because it is unclear if the patient is in need of the recited treatment (i.e., treatment of radiation induced enteritis) or is in need of the recited compound in the recited step of administration (i.e., administration of balsalazide). As a result, the patient intended to be circumscribed by the instantly claimed method is not clearly set forth in the claims such that it would have been immediately apparent to one of skill in the art the type of patient to be treated. Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection.

Should Applicant intend for independent claim 1 to circumscribe the treatment of a subject in need of treatment of radiation induced enteritis, it is unclear how dependent claims 2-3 or 7 properly limit the subject matter of instant claim 1. Each of dependent claims 2-3 or 7 circumscribe the administration of balsalazide to a patient for treating radiation-induced enteritis that has not yet undergone the radiotherapy that induced the enteritis. Thus, it is unclear how a patient can be treated for a disease caused by radiation exposure when the patient has not yet been exposed to the radiation that causes the disease. The claims are inconsistent in this regard and require appropriate clarification.

Similarly, though instant claim 13 defines the radiation induced enteritis as being caused by radiation therapy in combination with chemotherapy or a surgical procedure, instant claims 14-15 and 19 circumscribe the administration of balsalazide to a patient for treating radiation-induced enteritis caused by radiation in combination with chemotherapy or surgery where the patient has not yet experienced the radiotherapy, chemotherapy or surgery that causes the enteritis. Thus, it is again unclear how a patient can be treated for a disease caused by radiation exposure in combination with chemotherapy or surgery when the patient has (1) not yet been exposed to the radiation that causes the disease or (2) not yet been exposed to the chemotherapy and/or surgery that also contributes to the development of the disease. Clarification is again required.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 8 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The phrase “gastrointestinal malignancies, including colorectal, appendiceal, anal, or small bowel cancers” renders the claim indefinite because it is unclear if the enumerated malignancies following the

term "including" are intended to limit the claimed invention to those particular gastrointestinal cancers or if these malignancies are merely exemplary of the broader limitation of "gastrointestinal malignancies". As a result, the metes and bounds of the subject matter for which Applicant is presently seeking protection is not clearly defined and requires clarification. MPEP §2173.05(d).

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

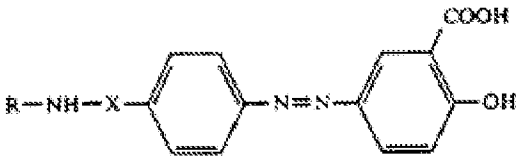
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 10 and 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. (WO 95/18622; 1995).

Johnson et al. teaches a method of treating a human suffering from colon cancer comprising administering to the human an effective amount of a pharmaceutical composition comprising a 2-hydroxy-5-phenylazobenzoic acid derivative compound of the formula



(p.12, l.19-25), wherein X is selected from, *inter alia*, a –CO- group and R is selected from, *inter alia*, a radical of the formula $-(CH_2)_n-Y-$, in which Y is selected from, *inter alia*, a carboxylic acid group, and n is a whole number from 1 to 6 (p.13, l.1-18), and further wherein the 2-hydroxy-5-phenylazobenzoic acid derivative compound is balsalazide (p.13, l.28-30). Johnson et al. teaches that the composition may be administered orally or rectally in a daily dosage

ranging from 1-14g per 70g body weight per day of the 2-hydroxy-5-phenylazobenzoic acid derivative (p.14, l.7-26). Note that the human suffering from colon cancer as disclosed in Johnson et al. meets Applicant's instantly claimed subject of instant claims 1 and 24-26, because the subject is clearly (i) suffering from colon cancer and (ii) in need of treatment with balsalazide, and is not disclosed as having received concurrent radiotherapy and, thus, meets the requirements of instant claims 2-3 (i.e., that the balsalazide is administered atleast 1 or 5 days prior to the first dose of radiotherapy) and instant claims 24-26 (i.e., that the balsalazide is administered before radiation therapy).

Though Johnson et al. does not explicitly teach the treatment of radiation induced enteritis via the administration of a therapeutically effective amount of balsalazide (claim 1), such a therapeutic effect would have been necessarily present in the method disclosed by Johnson et al. because Johnson et al. teaches a product that is identical to that instantly claimed for administration (i.e., a composition comprising a therapeutically effective amount of balsalazide in the amounts instantly claimed) to the same subject (i.e., a subject suffering from colon cancer) and, thus, must also possess this same newly recognized property described by Applicant, absent factual evidence to the contrary, because products of identical chemical composition used in an identical manner in an identical host cannot have mutually exclusive properties. MPEP §2112. Note, further, that the instantly claimed subject does not actually have to be exposed to radiotherapy that results in enteritis to meet the claims. This is evidenced by at least, e.g., instant claims 2-3, which circumscribe the administration of balsalazide to the patient before the patient even begins radiotherapy. Thus, there is no requirement that the patient must be identified as actually suffering from radiation induced enteritis, let alone be exposed to radiotherapy that causes the enteritis.

In re Best (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe includes functions and/or properties that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not

possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the newly cited function and/or property at the time of invention, so long as the function and/or property can be demonstrated to be reasonably expected to be present. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). The burden is now shifted to Applicant to prove that, in fact, Johnson et al. does not possess these same claimed characteristics.

Claim Rejections - 35 USC § 103

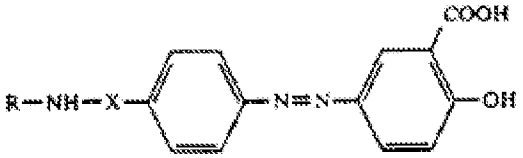
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-6, 8-13, 16-18 and 20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al. (WO 95/18622; 1995) in view of Podolsky (U.S. Patent Application Publication No. 2003/0078205; 2003).

Johnson et al. teaches a method of treating a human suffering from colon cancer comprising administering to the human an effective amount of a pharmaceutical composition comprising a 2-hydroxy-5-phenylazobenzoic acid derivative compound of the formula



(p.12, l.19-25), wherein X is selected from, *inter alia*, a –CO- group and R is selected from, *inter alia*, a radical of the formula $-(CH_2)_n-Y-$, in which Y is selected from, *inter alia*, a carboxylic acid group, and n is a whole number from 1 to 6 (p.13, l.1-18), and further wherein the 2-hydroxy-5-phenylazobenzoic acid derivative compound is balsalazide (p.13, l.28-30). Johnson et al. teaches that the composition may be administered orally or rectally in a daily dosage ranging from 1-14g per 70g body weight per day of the 2-hydroxy-5-phenylazobenzoic acid derivative (p.14, l.7-26).

Johnson et al. fails to teach (1) the concomitant application of radiotherapy to the subject with colon cancer and the resultant treatment of or protection against radiation induced enteritis, mucosal injury to the colon and/or colorectal inflammation (claims 1 and 24-26); or (2) the frequency and regimen of administration of balsalazide (claims 4-6, 9, 11, 16-18, 21 and 23).

Podolsky teaches that damage to the intestinal mucosa is especially prevalent when radiotherapy is delivered to a wide area of the abdomen for the treatment of colorectal cancer (p.7, para.[0094]). Podolsky further teaches that antineoplastic therapy, including chemotherapy and radiotherapy, damages the intestinal epithelium, resulting in proctitis, enteritis or mucositis (i.e., enteritis caused by chemotherapy and radiotherapy as recited in instant claim 13; p.7, para.[0094]).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the balsalazide chemotherapeutic regimen of Johnson et al. with radiotherapy to the abdomen for the treatment of a patient with colorectal cancer as disclosed by Podolsky becuase each was known to be an effective antineoplastic therapy for the treatment of colorectal cancer. The very fact that each was known to have a beneficial antineoplastic effect on colorectal cancer raises the reasonable expectation of success that the two therapies, when combined, would have, at minimum, additive, if not synergistic, effects in treating colorectal cancer. Please see *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980) ["It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."] and *In re Diamond and Kellman*, 149 USPQ562 (CCPA 1966).

Taking such teachings of Johnson et al. and Podolsky together, it would also have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the disclosed balsalazide formulation of Johnson et al. would have been reasonably expected to exert the same or substantially equivalent efficacy in the treatment of radiation-induced enteritis caused by radiotherapy in combination with chemotherapy in a patient suffering from colorectal cancer because: (1) the balsalazide composition of Johnson et al. was known to have efficacy in treating patients that suffer from colon cancer and radiation therapy was also known to have efficacy in treating patients that suffer from colon cancer as disclosed by Podolsky and, thus, the combination of the two therapies, each with the same therapeutic effect, for the treatment of colon cancer would have been *prima facie* obvious to the skilled artisan and (2) a significant proportion of patients that undergo radiotherapy to the abdomen for the treatment of, e.g., colorectal cancer experience damage to the intestinal mucosa that results in enteritis (i.e., radiation induced enteritis), as disclosed by Podolsky. Thus, Johnson et al. in view of Podolsky provides a clear

teaching, suggestion and/or motivation to combine the balsalazide composition of Johnson et al. with radiotherapy as disclosed by Podolsky for the treatment of colon cancer. Of this entire population of colon cancer patients to be treated with the balsalazide/radiotherapy combination, Podolsky provides the factual extrinsic evidence demonstrating that a subpopulation of patients receiving antineoplastic therapy in the form of chemotherapy and radiotherapy develop damage to the intestinal mucosa that results in enteritis and/or mucositis. Accordingly, the suggestion of Johnson et al. in view of Podolsky to use the claimed balsalazide/radiotherapy combination in any colon cancer patient is a clear suggestion to use it in any subpopulation of patients therein, such as those patients suffering from colon cancer and concomitantly suffering from enteritis caused by the applied radiotherapy and chemotherapy combination, with the reasonable expectation of the same (or at least substantially equivalent) level of efficacy in treating this subpopulation of patients with radiation induced enteritis and colon cancer as would be expected in the treatment of colon cancer patients *per se*. Furthermore, since products of identical composition cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same host, whatever effect(s) the instantly claimed balsalazide formulation has in treating or protecting against radiation induced enteritis must necessarily be present in the method of Johnson et al. taken in view of Podolsky. See MPEP §2112.

Regarding the instantly claimed regimen of administration of balsalazide (i.e., for at least one or for 14 days after cessation of radiation therapy as in instant claims 5-6 or 17-18; twice daily as in instant claims 9 and 21; or administered from between about 8 weeks to about 12 weeks as in instant claims 11 and 23), the determination of the most optimal regimen of administration would have been well within the skill of the artisan at the time of the invention and would not have required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included, but not have been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease,

route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination, as well as toxic reactions to radiotherapy, tolerability of the radiotherapy and chemotherapy and the duration of toxic effects of the treatment, even after conclusion of such treatments. Thus, the dosage regimen and/or frequency of administration that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which is presently claimed.

Conclusion

Rejection of claims 1-26 is proper.

No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP §714.02 and §2163.06). Note that support should be provided for amendments to previously pending claims, as well as any newly added claims. In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, not the published application. Due to the procedure outlined in MPEP §2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. §102 or 35 U.S.C. §103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action in order to assist the examiner with double patenting analysis in the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

August 11, 2011